Witness Name: John Collinge

Statement No.: WITN3093002

Exhibits: WITN3093003-WITN3093028

Dated: 26 April 2022

**INFECTED BLOOD INQUIRY**

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**SECOND WRITTEN STATEMENT OF JOHN COLLINGE**

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I provide this statement in response to a request under Rule 9 Request of the Inquiry Rules 2006 dated 19 November 2021.

I, John Collinge, will say as follows:

## Section 1: Introduction

1. **Please set out your name, address, date of birth and professional qualifications.**

My name is Professor John Collinge and my address is: MRC Prion Unit and Institute of Prion Diseases at UCL, Courtauld Building, 33 Cleveland Street, London W1W 7FF. My date of birth is GRO-C 1958. My professional qualifications are: BSc, MB ChB, MD, DSc (Hon), FRCP, FRCPath, FMedSci, FRS.

2. **Please set out your employment history including the various roles and responsibilities that you have held throughout your career which relate to the Inquiry's Terms of Reference, as well as the dates.**

I qualified in Medicine from the University of Bristol in 1984 and underwent postgraduate training in medicine and neurology before being appointed an Honorary Consultant in Neurology at St. Mary's Hospital in London in 1994 where I was also a Wellcome Trust Senior Fellow in the Clinical Sciences and (from 1996) a Wellcome Trust Principal Fellow in the Clinical Sciences at the Imperial College School of Medicine. I was appointed to a personal Chair at Imperial College in 1994. I established a specialist NHS clinic for prion disease at St Mary's Hospital which was later designated the NHS National Prion Clinic. In 1998, I founded and established the Medical Research Council (MRC) Prion

Unit at Imperial College School of Medicine at St Mary's with a national strategic role in prion research. I relocated, together with the MRC Unit and NHS National Prion Clinic, to the UCL Institute of Neurology and National Hospital for Neurology and Neurology (part of UCLH NHS Foundation Trust) at Queen Square London in 2001. I was appointed to an established chair in neurology at UCL in 2001 and founded and headed the University Department of Neurodegenerative Disease. In 2017, the MRC Unit, in line with MRC policy, became a part of UCL and was renamed the MRC Prion Unit at UCL. As part of this change, I left the Institute of Neurology to establish a new UCL Institute of Prion Disease within which the MRC Prion Unit at UCL now sits. My current appointments are as Professor of Neurology at University College London (UCL), Honorary Consultant Neurologist and Director of the NHS National Prion Clinic at the National Hospital for Neurology and Neurosurgery, UCLH NHS Foundation Trust and Director of the MRC Prion Unit and Institute of Prion Diseases at UCL. I am a member of the UCL Academic Board and UCL Faculty of Brain Sciences and UCL Institute of Neurology Executive Committees. I have been a Senior Investigator of the Faculty of the National Institute for Health Research (NIHR) since its inception in 2008 (now Senior Investigator Emeritus). I served on the Council of the Royal Society (representing Health and Human Sciences) from 2011-13. In 2013, I was elected an Honorary Fellow of the American Neurological Association and in 2017 I was appointed visiting Professor of Neurology at Harvard Medical School, USA. I am also a Director and Shareholder of D-Gen Limited. This is an academic spin-out company founded at Imperial College London in 2000 and jointly owned by a number of academic institutions including the MRC, UCL and the Wellcome Trust together with the founder scientists including myself. I do not receive any remuneration from the company.

I wish to make clear that I am providing this statement in my own capacity. The views I express are my own and may not be the views of the institutions I am currently, or have been, employed by, or the organisations who fund the research my team undertake.

The IBI team visited the MRC Prion Unit on 31 May 2019 to inspect and take copies of potentially relevant paper documents located by my office at the Unit and NHS Prion Clinic.

3. **In earlier correspondence with the Inquiry you provided a list of your relevant committee memberships. For your reference, these are included in Schedule B at the end of this R9 document. Please briefly describe the nature of your involvement in these committees. If there are any further associations, parties, societies or groups relevant to the Inquiry's Terms of Reference, also include them here.**

I served as a member of the UK Government Spongiform Encephalopathy Advisory Committee (SEAC) from 1996-2002 and from 2007-2010. This provided high-level advice to MAFF (subsequently DEFRA) and the Department of Health (now DHSC). I also served as a member of the Department of Health (DoH) /MRC Steering Group for Studies of Detectable PrPSc, the DoH CJD Tissue Management Steering Group (2002 – 2007), the DoH CJD Therapy Group (2002 – 2004) and the MRC New Therapies Scrutiny Group (2005). I served as Deputy Chair of the European Union High-level group on Bovine Spongiform Encephalopathy (BSE) (1996) which formulated a comprehensive scientific research strategy for the EU and which reported directly to the EU Agriculture Commissioner. I was a member of the TSE group, Scientific Steering Committee of the European Union (2001 – 2003). I have led or been a member of multiple EU research consortia or collaborations in prion disease. I have also

served on various World Health Organisation (WHO) groups on transmissible spongiform encephalopathies (prion disease). I am a member of the CJD International Support Alliance (CJDISA) Friends and Advisors Group. I am a Committee member of the CIDRAP CWD (Chronic Wasting Disease, an epidemic prion disease of cervids) Response, Research and Policy Program Expert Advisory Group.

4. **Please provide an outline of any relevant relationships you had, or initiatives you were involved in to ensure that the UK Government, Blood Services, UKHCDO, NHS bodies, medical profession and patients were informed and educated about the risks of vCJD transmission via blood and blood products.**

In addition to the extensive and long-term committee work outlined above, I also advised the then Secretary of State for Health (the late Rt Hon Frank Dobson MP) in 1997/1998 directly at his request on risks of transmission of vCJD by blood and blood products. I discussed recent evidence from my laboratory of widespread prion infection of lymphoreticular tissues in patients with vCJD (which was in marked contrast to classical or sporadic CJD where infection is largely confined to the central nervous system) together with available data from other laboratories of infectivity of blood components in animal models and the likelihood in my view that vCJD would be transmissible by blood and blood products. I advised introducing leukodepletion of blood to reduce risks of transmission of vCJD by transfusion and the SoS took a decision that day to introduce leukodepletion and agreed this with the then Prime Minister, Mr Tony Blair. Mr Dobson asked that I return to the Department that afternoon to support the Chief Medical Officer (CMO; Sir Kenneth Calman) at a press conference where the decision would be announced. I have had many *ad hoc* meetings with successive Chief Medical Officers (Sir Kenneth Calman, Sir Liam Donaldson, Professor Dame Sally Davies, Professor Sir Chris Whitty) and other Government Officials since 1996 to discuss research into prion diseases and public health. I had multiple meetings with officials from the NHS National Blood Service and Health Protection Agency/Public Health England and shared our data. The National Prion Clinic liaised regularly with the National CJD Surveillance Unit in Edinburgh and has monthly meetings to ensure both Units are aware of all patients and to share results of investigations and clinical samples as necessary.

My research Unit has conducted multiple research projects on vCJD relevant to risks of its transmission by blood and blood products. We were involved in identification and publication of the first cases of what became known as vCJD and demonstrated that it was caused by the BSE prion strain in 1996. We discovered and described the involvement of the lymphoreticular system in vCJD which raised concerns about the potential for blood-borne infectivity, and which led to our development of tonsil biopsy for the diagnosis of vCJD and to my suggestion to DoH that anonymous screens of tonsils removed during routine surgery (later extended to include archived appendix tissue removed during surgery for appendicitis) might allow estimates of the population prevalence of silent or carrier infection with vCJD prions to guide public health risk assessments. We subsequently developed and published a blood test for vCJD and a method to prion-decontaminate surgical instruments. We also performed fundamental research to underpin development of effective therapeutics for prion disease which could be used to block the development of disease in those accidentally infected with prions, for example by prion-contaminated blood and blood products. All this work was published in the scientific and medical literature, often in prominent journals and associated with press releases and multiple interviews to print and broadcast media. I generally briefed Government officials and patient

advocates or organisations prior to publication of important findings. I gave many seminars and lectures on this subject nationally and internationally to scientific and clinical audiences and conferences and to patient and lay groups including public lectures. My Unit has held annual open days for anyone interested for many years to which we invite patients, families, carers, health professionals, colleagues from the Edinburgh CJD Surveillance Unit and public health bodies, Government and Research Council officials and interested Parliamentarians. I personally give a research update and take any questions over a 2-3 hour period at each open day. I have spoken many times at patient support and advocacy organisations nationally and internationally to communicate our work and answer questions. These issues were also discussed in open session at the House of Commons Science and Technology Select Committee Inquiry into vCJD and blood where I gave written and oral evidence (see below). The MRC Unit and the National Prion Clinic have dedicated websites with detailed information about our research and clinical services for professional and lay audiences (see www.nationalprionclinic.org and www.ucl.ac.uk/prion).

On the advice of the former Chief Medical Officer, Sir Liam Donaldson, who had visited my Unit to get an update on CJD research (and during which we discussed the very worrying finding published by the Health Protection Agency suggesting around 1 in 2000 of the UK population may be silently infected with prions), I wrote to the UK Government Chief Scientific Advisor, Sir Mark Walport, on 18th November 2013. I conveyed my concerns that the publicly funded research my Unit and others have done (at the direct request of Government) to find effective solutions to these problems – effective prion decontamination of surgical instruments, a prototype vCJD blood test, and treatments – continue to face major barriers to translation to the NHS. I asked for a meeting to discuss these issues and seek his advice on possible ways ahead. He replied in early January (letter undated but presumably 2014) to say that he had been in touch with DoH and was satisfied these matters were being taken very seriously. He also noted the forthcoming House of Commons Select Committee inquiry and looked forward to its findings but declined to meet with me.

5. **The Inquiry is aware that you provided evidence to the Parliamentary Inquiry on blood, tissue and organ screening for vCJD in 2013/2014 (NCRU0000320_005; TSTC0000051). Please review the statements and views you expressed to the Inquiry and set out whether your views have changed in any way. If your views have changed since making the statement please explain how they have changed and why.**

I have reviewed the two documents provided (NCRU0000320_005; TSTC0000051) and my views remain essentially unchanged with the exception that the absence of identified cases of primary or secondary vCJD in recent years (since 2015) suggests that the considerable uncertainty in 2013/14 in predicting the public health consequences of the concerning estimates from screening of archived appendix tissue by the Health Protection Agency (that around 1 in 2000 of the UK population may be silently infected with vCJD prions) can now be revised downwards. The advice to DoH to leukodeplete donor blood, based on the best evidence available in 1997, was in the expectation that it would significantly reduce but not eliminate the risk of vCJD transmission, but I have been particularly pleased that no cases of secondary vCJD from blood transfusion have been identified so far as I am aware since leukodepletion of donor blood suggesting this step may have completely interrupted a secondary epidemic. I noted in my evidence in 2013/14 that we should remain alert to the possibility

that a proportion of the rising number of patients identified with classical sporadic CJD (sCJD) in the UK may in fact be BSE-related given our research from animal models suggesting that BSE/vCJD prions can trigger propagation of prion strains seen in sCJD as well as vCJD. Recorded case numbers of sCJD continue to rise and this should still be a consideration and the HPA finding of 1 in 2000 positive appendix samples remains unexplained (see below).

6. **Please confirm whether you have provided evidence or have been involved in any other inquiries, investigations, criminal or civil litigation in relation to the human immunodeficiency virus ("HIV") and/or hepatitis B virus ("HBV") and/or hepatitis C virus ("HCV") infections and/or variant Creutzfeldt-Jakob disease ("vCJD") in blood and/or blood products. Please provide details of your involvement.**

I have already provided the Inquiry with a statement (WITN3093001) in reference to a patient who had developed iatrogenic vCJD following blood transfusion in response to a request under rule 9 of the Inquiry rules 2006 dated 25th April 2019.

**Section 2: Knowledge of risk**

**The Inquiry is investigating how knowledge of the risk of vCJD developed over time within the UK Government, Blood Services, Haemophilia Centres and other NHS organisations. The Inquiry is aware of your work in the initial discovery of vCJD (HSOC0010099), determining its involvement with the lymphoreticular tissues (MHRA0021347) and the development of screening and diagnostic tests (DHSC0004747_040; NHBT0033626).**

7. **In a meeting between yourself and Lord Privy Seal in November 1996, you indicated that "there is no suggestion that transmission can occur from human to human" (CABO0000179_002). Did this encompass human to human transmission via blood or blood products? If yes, was this the accepted view at the time?**

I do not recall the precise discussion and have not seen these minutes previously but what I was saying is that CJD is not contagious – that is it cannot be transmitted from person to person by social or even intimate contact. Rather, transmission of human prion disease had only been seen following ingestion of infected human tissue (as in the case of kuru in Papua New Guinea as mentioned in the minute) or accidental inoculation with human prions during medical or surgical procedures (causing iatrogenic CJD). I do not recall any specific discussions on transmission by blood or blood products.

8. **Also in this meeting (CABO0000179_002), it is stated "many members of SEAC are complacent about the low risk of an epidemic; Professor Collinge (and some**

**other newer members) feel this is misplaced". Please explain the rationale for your view.**

At that time, in 1996, we had established that the emerging cases of vCJD were caused by the same prion strain as that causing epidemic BSE in cattle (MHRA0021347). It was known that many hundreds of thousands of BSE-infected cattle entered the human food chain prior to the introduction of the specified bovine offal orders and that such orders were in any case incompletely enforced up to 1996. We did not know what amount of BSE-infected tissue would need to be ingested to cause the disease in humans (that is we did not know the oral lethal dose of BSE prions); this would be determined by the so-called "species barrier" effect which we could not quantify in humans. In mice and sheep, where it could be experimentally quantified, oral transmission of BSE was comparatively easy. While a species barrier effect limiting transmission of BSE to humans would be present and probably prevent a huge epidemic, that tens of thousands for example might develop vCJD (albeit spread over many years) in the UK was certainly possible. My view was that we needed to work on that basis in terms of reviewing measures to protect the public health - and in particular with respect to relevance to this Inquiry - and to introduce measures to limit a secondary epidemic by iatrogenic routes (medical and surgical procedures including blood and blood products).

9. **In a July 1999 Lancet article, you stated that, "the risks from blood and blood products... cannot be quantified" (CABO0000340_003, page 6; later discussed in parliament NHBT0002490, page 8). Please explain the rationale behind this view.**

Quantification of the risks of transmission of vCJD by blood and blood products would have required methods to determine the number of infectious prions in a defined volume of blood or blood product and knowledge of what dose of infectious prions would have to be administered by particular routes in order to initiate an infection in the human recipient. No such human prion bioassay existed and determining the human lethal dose would require deliberate infection of humans with defined doses which was obviously unethical. Experiments were done in animal models to address these questions but extrapolation to humans is fraught with difficulties given the marked differences between the species in key parameters likely to be important such that animal data could be very misleading. An alternate and ethical approach to assess risk, albeit without quantification as such, was from epidemiological studies but no such data were available at that time.

10. **In an undated letter, you are noted to have had the view that, "there is a higher risk of vCJD from blood transfusions than we [The Department of Health] are prepared to admit" (DHSC0004223_062).**
    a. **Was this always your view throughout the key period (1985present)?**
    b. **What were the reasons, in so far as you understood them, for the reluctance of the Department of Health to accept this?**

This DoH note (DHSC0004223_062) is not only undated but also is not on headed paper and the author and recipient are only identified by their first names. I presume that the recipient (Patricia) was the then Secretary of State for Health (SoS), Rt Hon Patricia Hewitt MP. I had first written to DoH (both to the then CMO Sir Liam Donaldson and the then Director of Research and Development, Professor Sally Davies) in September and December 2004 [WITN3093003] respectively regarding the level of risk and counselling of patients identified as receiving blood transfusions from vCJD infected donors. In January 2006, I wrote again to Sir Liam Donaldson to express my concerns that recipients of blood transfusion from a vCJD infected donor were at significant risk but not necessarily aware of the specialist NHS service, the National Prion Clinic, which could support them and indeed offer access to a clinical trial of a potential therapeutic if found to be vCJD prion-infected (DHSC0004223_065 and 066). The author of the note appears to advise the SoS that current arrangements were considered satisfactory.

**Section 3: Response**

11. **What avenues or reporting procedures were in place to enable you and your colleagues to disseminate the information you had about the risk of vCJD from blood and blood products to the medical, and patient communities?**

Our research work is published in the scientific and medical literature, often in prominent journals and associated with press releases. I have given multiple interviews to print and broadcast media. We also provide updates on our research on our academic (www.ucl.ac.uk/prion/) and clinic (www.nationalprionclinic.org) websites. I generally briefed Government health officials and patient advocates or organisations prior to publication of important findings. We have regular joint coordination meetings with the National CJD Research and Surveillance Unit (NCJDSU) in Edinburgh. I gave many seminars and lectures on this subject nationally and internationally to scientific and clinical audiences and at conferences and to patient and lay groups including public lectures. My Unit has held annual open days for anyone interested for many years to which we invite patients, families, carers, health professionals, colleagues from the NCJDSU and public health bodies, Government and research council officials and interested Parliamentarians. I personally give a research update and take any questions over a 2-3 hour period at each open day. I have spoken many times at patient support and advocacy organisations nationally and internationally to communicate our work and answer questions.

12. **What role did you have in advising on risk reduction measures? What measures have you advised should be put in place over the years? You may wish to comment on the following measures:**

    a. **Donor selection and exclusion policies**
    b. **Importation of plasma from the USA and elsewhere**
    c. **Leucodepletion and prion filtration (MHRA0020531, page 10)**
    d. **Product withdrawal, quarantine and recall**
    e. **Recombinant blood products**

f. **Promotion of blood alternatives**

g. **Surveillance infrastructure**

h. **Development of Screening and Diagnostic Tests (section 4 covers this in greater detail)**

My principal advisory role was as a member of SEAC where these issues were discussed on multiple occasions. My direct involvement was in advising on measures c (Leukodepletion) and h (Development of Screening and Diagnostic Tests). As mentioned above in response to question 4, I directly advised the then Secretary of State for Health (the late Rt Hon Frank Dobson) in 1997/1998 at his request on risks of transmission of vCJD by blood and blood products and recommended the Government consider leukodepletion of donor blood. My laboratory discovered and reported the prominent lymphoreticular system involvement in vCJD. I advised the Government this could allow surgical tissue screening studies to estimate prevalence of clinically silent vCJD infection in the community. I was involved in developing diagnostic tests, notably a blood test for vCJD (see below).

13. **In your view, was the Government receptive and responsive to scientific advice offered by SEAC and any other committees you were a member of that advised on vCJD and blood?**

Generally yes regarding committees I was a member of. However, SEAC had a broad, high-level, advisory role and there were other committees (separate from SEAC) such as SaBTO advising specifically on blood and blood products that I was not a member of.

14. **Do you consider that the implemented risk reduction measures were sufficient and timely? If not, why not and what else could have been done (or done earlier) to reduce risk?**

The introduction of universal leukodepletion of donor blood was introduced in a timely fashion by the then Secretary of State, Rt Hon Frank Dobson MP, and now appears to have been highly effective in prevention of secondary transmission of vCJD prions. It also brought other benefits in terms of reduction of viral transmission, graft vs host reactions and increasing shelf life.

The obvious tool that would in principle have enabled accurate risk assessment and risk management was a highly specific blood test capable of detecting healthy but infected individuals. The early introduction of such a donor screening test for vCJD prion infection might have allowed more specific risk reduction and provided the data to assess the need for the major, expensive and disruptive additional measures that were introduced (including the ban on use of UK plasma to make plasma products (importing instead from US), importing blood products for those born after 1996 (assumed not to be BSE-exposed) and banning recipients of blood transfusions since 1980 being blood donors) which were of uncertain efficacy or necessity. However, producing such a blood test turned out to be much more scientifically and technically challenging than originally envisaged and multiple academic groups and diagnostics companies failed to deliver such a test. My Unit did develop a blood test (called

the Direct Detection Assay or DDA) and published this as a fast-track article in the *Lancet* in 2011. This is discussed in more detail below.

## Section 4: Screening and Diagnostics Tests

15. **What tests are available to those who have been notified that they are at risk of vCJD?**

There are a series of tests that can be performed to investigate patients *showing symptoms and signs of disease* and in whom vCJD is considered a possible diagnosis. Such tests which can be used to diagnose vCJD and to exclude other conditions include a range of blood tests, MRI brain scan, electroencephalogram, cerebrospinal fluid and genetic tests. Tonsil biopsy and the Direct Detection Assay (DDA) blood test can be used for specific diagnosis of vCJD. However, individuals notified that they are at risk of vCJD will generally not have symptoms or signs suggestive of neurological disease and would not be routinely investigated with such tests. Healthy individuals would be given reassurance and offered counselling where appropriate and also long term follow up if the risk justified this. At present, there is no test that can exclude asymptomatic vCJD prion infection in such individuals. The DDA blood test can be used to diagnose vCJD in symptomatic individuals but it is not known how sensitive it is in detecting infected, but asymptomatic, individuals. For this reason, we do not offer this test in that context as a negative result cannot be interpreted. Such a test will however be important if effective treatments become available as a positive test could allow early therapeutic intervention to prevent disease onset.

In part, in response to the recognition of blood transfusion associated iatrogenic vCJD we were funded by the MRC in 2007 to develop a therapeutic anti-PrP monoclonal antibody. My Unit had already validated the normal cellular prion protein ($PrP^C$) as a therapeutic target showing it could be targeted in adult laboratory mice without consequence (Mallucci et al EMBO J 2002) and that this completely blocked the development of prion disease (Mallucci et al *Science* 2003). We also showed a therapeutic proof of principle of treating prion infection in mice using a monoclonal antibody (White et al *Nature* 2003). The development of a humanised monoclonal antibody drug was aimed both at treating established neurological disease and also for post-exposure prophylaxis in those iatrogenically or accidentally exposed to prions. Treating established neurological disease was expected to be challenging in part because antibodies do not readily enter the brain (due to the so-called blood brain barrier). However, intravenous treatment with such an antibody should be highly effective at eradicating peripheral (LRS) prion infection before the infection has reached the brain. We successfully produced a fully humanised therapeutic antibody (PRN100) and have recently delivered the first rationally-designed experimental treatment for human prion disease in a small number of CJD patients with progressive neurological disease. The treatment appeared to be safe and achieved encouraging cerebrospinal fluid (CSF) and brain tissue levels of PRN100. Our findings have recently been published (Mead et al *Lancet Neurology* 2022) [WITN3093004] and we feel they justify the need for formal efficacy trials in CJD patients at the earliest possible clinical stages and as prophylaxis in those at-risk of prion disease due to gene mutation or accidental or iatrogenic prion exposure.

16. **It is our understanding that in 1996, you informed SEAC that you attended an FDA meeting where "the need for experimental means for testing blood products had**

**been emphasised" (CABO0000579_001, page 5). In 1997, you were conducting an initial investigation into prion detection in blood (NHBT0005417_002, page 4). In 1999, you are cited to have indicated a blood test for vCJD could be available in 2-3 years (NHBT0004118_004). In 2000, you reiterated the need for a "simple, reliable blood test for population screening" (NHBT0087384)**

a. **Please add to or correct this timeline if it is inaccurate or missing key actions or developments in relation to your efforts to introduce a test.**

b. **What were the reasons for the blood test not being developed until 2011? Please consider any challenges, whether scientific, ethical, financial, political or other which delayed the test's development.**

I recall attending an FDA meeting in Washington but have no independent recollection of the content of the meeting and my office has been unable to find any minute or other related documents. Once we had discovered the extensive lymphoreticular tissue involvement in vCJD patients in 1996/7 we were very concerned at the risks of transmission of vCJD prion infection by blood and blood products and considered development of a blood test which could be used to screen donor blood and exclude infected donations was a high priority. In addition, it was important to have a test that could be used to aid early diagnosis of patients without the need for a tissue biopsy. We began to consider research approaches to this at the MRC Unit at an early stage, as did other academic research groups and commercial diagnostics companies worldwide. Whilst the need for a blood test was widely accepted, the scientific challenges were however formidable. The usual methods to determine whether an individual was infected with a conventional infectious agent (such as a virus) were by: detecting specific antibodies in blood (indicative of an immune response to the virus); by detecting presence of genomic material (DNA or RNA) of the virus by a technique called PCR; or by detecting viral antigens such as proteins specific to the virus (and therefore not otherwise present in the patient) using specific antibodies developed in the laboratory that bind to those proteins.

However, in the case of prions, there is no agent genome (DNA or RNA) to detect by PCR (prions lack their own genome and are simply composed of protein). Prions are assemblies of a misfolded form of one of the body's own proteins, known as prion protein (or $PrP^{C}$: short for *cellular* prion protein). As these disease-related forms of prion protein (which form long fibres or rod-like structures, technically known as amyloid) are formed from one of the body's own proteins the immune system does not recognise them as foreign in the same way it would a viral or bacterial protein. This phenomenon is called *immune tolerance*, a natural process that prevents our immune system attacking our own cells. Furthermore, the misshapen prion proteins that form the prions are chemically identical to the normal prion protein present naturally on our cells. The $PrP^{C}$ in a blood sample is also present at a much higher level than the disease-associated prion protein assemblies that constitute the infectious prions.

We and others had developed antibodies against the human prion protein in the laboratory but these did not generally distinguish between the body's normal cellular prion protein ($PrP^{C}$) and the disease-associated forms (generally called $PrP^{Sc}$). Detection of $PrP^{Sc}$ is considered pathognomonic of prion

infection or disease and so is an excellent diagnostic marker. $PrP^{Sc}$ can however be differentiated from $PrP^{C}$ as it is more resistant to being broken down by proteolytic enzymes, classically an enzyme called proteinase K (PK). Looking for PK-resistant PrP was in specialist use at that time for diagnosis and worked very well on brain or tonsil tissue. However, infectious prions are present in vCJD blood at levels that are orders of magnitude lower than in brain tissue and such methods were far more challenging in blood due to the low level of $PrP^{Sc}$ compared to $PrP^{C}$ and also because other components in blood interfered with those sorts of tests. We and others were unable to detect $PrP^{Sc}$ in blood using those methods. In addition, emerging research work indicated that only a minority of infectious prions had the classical level of PK-resistance associated with $PrP^{Sc}$. Any useful diagnostic blood test would have to not only be extremely sensitive in detecting disease-related PrP but also highly specific for abnormal PrP against a background of normal $PrP^{C}$ and also the use of PK turned out to be of limited value as it destroyed many disease-related PrP forms as well as $PrP^{C}$.

Much subsequent work was done by us and other academic groups and commercial organisations around the world to develop antibodies that distinguished between $PrP^{C}$ and $PrP^{Sc}$ but advances were not sufficient to detect prions in blood at the sensitivities required. In our own work, we were able to considerably improve our immunoassays using novel antibody combinations (for example see Tattum et al, A highly sensitive immunoassay for the detection of prion-infected material in whole blood without the use of proteinase K. *Transfusion* 50; 2619-27 (2010)). Other methods being developed included attempts to amplify prions in test tube experiments using a newly developed technique called Protein Misfolding Cyclic Amplification (PMCA) but this presented significant technical problems (in particular there was a high likelihood of false positives) and the methods were highly time consuming (taking several days).

The real breakthrough for us came via another research project in the Unit which was trying to develop new methods to sterilise surgical and medical instruments that may have been contaminated with prions during normal use. It had been known for many years that prions could attach to surgical instruments and that prions are relatively resistant to normal hospital sterilisation methods. This led to the risk of patient-to-patient transfer of CJD prions, resulting in so-called *iatrogenic CJD*. The recognition of vCJD and the possibility both that many in the UK population might be silently infected with prions following dietary exposure to BSE and that other tissues in the body in addition to the central nervous system (potentially including blood) were infected in patients with vCJD led to considerably increased concerns in this regard. The Department of Health launched a major research programme and funded many research groups, including ourselves, to develop novel methods to solve this problem. My Unit demonstrated that indeed prions bound avidly to stainless steel and that prion-contaminated steel wires could very readily infect laboratory mice even after extensive washing. The Unit undertook a major research project to develop methods to sterilise prions on metal surfaces that could be adapted to routine hospital use and to develop novel assays that could quantitatively validate efficacy in reduction of infectivity. This was successfully achieved with the development and validation of an enzyme mix formulation that could be used as a pre-wash to eliminate prions prior to normal hospital sterilisation processes. This was subsequently developed by DuPont into a product called *Rely-On PI* but not used by the NHS: a subject covered in detail in the House of Commons Select Committee report into vCJD and blood.

In the course of this parallel research project, we were surprised at just how avidly prions attached to metal wires and yet retained their infectivity. We then considered whether we could exploit this phenomenon to improve the sensitivity of a blood test by first concentrating prions from a blood sample on a metal surface which could then be immunoassayed using specific antibodies we had already developed. We explored many types of metal and plastics to see what worked best and found that a particular type of stainless steel bound prions most avidly. This could be obtained in a powdered form which provided a large surface area for prion binding and was used as a solid-state binding matrix to

concentrate prions from a blood sample which could then be held by a magnet allowing separation from other components. This was developed into an assay which was around 10,000 times more sensitive than anything hitherto available and which indeed was able to detect prions from vCJD brain tissue diluted 10 billion-fold suggesting it was able to detect at around the level of single infectious particles. Indeed, this assay was positive in 15 of the 21 blood samples from vCJD cases we had access to, but was negative in all samples from normal individuals or those with other neurological conditions. This gave a test sensitivity of 71% and specificity of 100%. We submitted these data on what we considered a prototype blood test to the *Lancet* for fast-track peer review and it was published soon after as the journal cover article on February 5th 2011 (NHBT0033626).

The principal reasons therefore for the length of time taken to develop the prototype test were the scientific challenges, which were considerable, and of which only a brief overview are given here.

17. **What subsequent research was proposed following the development of the blood test in 2011? Please describe any discussions you had with the Department of Health, Medical Research Council and Government regarding funding for these proposals (DHNI0000164; CVHB0000006_009; TSTC0000047 (page 19); TSTC0000046 (page 19)).**

**What were the outcomes of these discussions and proposals?**

**Background**

Our data published in *Lancet* in 2011 demonstrated that our test could be used to help diagnose patients with neurological illness in whom vCJD was suspected. We immediately hoped that the test would allow earlier diagnosis of vCJD, which often had a clinical onset that could be confused with other much more common conditions. Early diagnosis could avoid unnecessary other tests and allow access to clinical trials at an early clinical stage before extensive irreversible brain damage had occurred. We went on to test larger numbers of other neurological diseases and to further evaluate the prototype test in service at the National Hospital for Neurology and Neurosurgery using our existing funding.

Our prototype test had of course also been developed with a view to its use in public health risk assessment and risk management. A sensitive and specific blood test could be used in prevalence studies to estimate the extent of blood-borne vCJD prion infection in the UK population and then to reduce or remove risk of secondary transmission of vCJD prions via use of blood and blood products by screening donor blood. Much further work would be required however to achieve this. While we had already demonstrated the test sensitivity in vCJD patient samples and showed that the prototype test had a very high analytical sensitivity using blood samples "spiked" with vCJD patient tissue, the key next question was its specificity. This needed to be extremely high to be useful as a donor screening test to avoid false positives (as it would be used on many thousands of blood donations), and also a significant false positive rate would mean that prevalence studies would have to be extremely large to produce statistically meaningful results.

In humans, prion infections have highly prolonged, clinically silent, incubation periods typically spanning years. It was of course hoped that our test could detect vCJD infection not only at an early clinical stage but in asymptomatic people infected with (or at risk of infection with) vCJD prions. If this

were possible, our prototype could form the basis for a screening test on donated blood to prevent iatrogenic transmission of vCJD prions by blood transfusion or blood products. It would also allow a preliminary estimation of the prevalence of vCJD prion infection amongst the UK population to inform public health risk assessment. More detailed follow up studies on prevalence could then be carried out by public health bodies with statutory responsibility and epidemiology expertise, notably with respect to blood donation. Determining directly whether our prototype test could detect healthy carriers of infection was difficult as we only had access to blood samples from patients who were clinically affected. So far as we were aware at the time (however, see below) there were no blood samples taken from healthy individuals who went on to develop vCJD available to test and there was no other method to identify healthy carriers of infection. Consequently, we had no blood samples to directly investigate whether our test could identify carriers of vCJD.

We already knew, as mentioned above, that our test had an extremely high analytical sensitivity. Indeed, it was possible our test was detecting close to, or even below (as a prion is a large assembly of PrP molecules and can break down into smaller assemblies), the level of single infectious particles since it could detect $10^{-10}$ dilutions of infected brain tissue. Consequently, it was plausible that preclinical detection would be possible using the prototype test or developments of it.

In the absence of blood samples from known carriers, the next research step we planned was to use our prototype test on a large series of blood samples from a country with low or negligible exposure to BSE. The US Red Cross were kindly willing to supply samples from 5000 US blood donors. If all these samples were negative using our test it would imply it had a high specificity (low risk of false positives). Assuming those results were encouraging, the next step would be to compare a much larger number of UK samples with a similar number of US samples. At the time it had been estimated, based on anonymous screening of surgical tonsil and appendix samples, that around 1 in 4000 of the UK population may be infected with vCJD (later refined by HPA following a larger screen of surgical appendix tissues to 1 in 2000). If we saw a significant number of positives in the UK samples but again zero in the US donor samples that would indicate both that the test was indeed sensitive enough to detect healthy carriers and also that it retained a very high specificity. It would also confirm that there was indeed significant prionaemia in the UK population (although suitably designed population studies by others with relevant expertise would be necessary to provide formal prevalence estimates). Such evidence would establish that the prototype test could indeed form the basis of a screening test for donor blood. However, it was clear that our prototype test was not suitable for large-scale donor screening by the Blood Service and would require technical development necessary to produce a practical high-throughput test from our laboratory prototype. This was outside our expertise and would require a commercial diagnostics company.

**Discussions with DoH, MRC and Government**

Cognisant of the potential public health importance of our work, I kept officials at the Department of Health, including the then CMO, Sir Liam Donaldson, informed of progress on our work to develop a vCJD blood test through meetings with their officials. Two very senior DoH officials (David Harper and Clara Swinson) had visited my Unit in May 2010 to get an update on our research and I shared with them our progress at that time. I also offered to brief the new CMO, Dame Sally Davies, but she was unable to meet with me at that time. I also kept the MRC CEO updated on our progress and on his advice wrote to Dame Sally on 3rd December 2010 (in advance of the publication of our paper in the *Lancet* in February 2011). Given the importance of these matters, I also wrote to the then Secretary of State for Health, Rt Hon Andrew Lansley MP on the same day and offered to brief both of them personally on our progress [WITN3093005]. The Secretary of State replied to thank me for notifying him, welcoming

the scientific progress and asking me to keep the CMO informed and to continue to work closely with Departmental officials.

I had also had discussions with two senior Parliamentarians, the late Rt Hon Frank Dobson MP (our constituency MP) and Sir Paul Beresford MP (a practicing dentist with a strong interest in CJD and patient safety) both of whom had a long-term interest in our work and who regularly attended our Unit open days.

Given the potential for our vCJD blood test to be adapted in principle to screen for prion infection in other mammalian species, I also wrote to the then Chief Veterinary Officer, Dr Gibbens, at the Department for Environment, Food and Rural Affairs (DEFRA) to notify him of our breakthrough. Again, I offered a briefing to share our data at that time. The Unit diagnostics team leader, Dr Graham Jackson, and I subsequently met with DEFRA officials on 18th February 2011.

Our paper was scheduled for publication in the *Lancet* on 5th February 2011 and MRC issued a Press Release under embargo until 3rd February: "World's first blood test for vCJD developed in MRC lab". I updated Sir John Savill (MRC CEO) on 3rd February 2011 and outlined to him what I considered to be the important next steps: These were: (1) further studies on its diagnostic use in differential diagnosis in suspect cases – I explained that this work was proceeding using existing funding; (2) its application to address public health issues. I explained that: the prevalence of clinically silent vCJD prion infection in the UK following population-wide BSE exposure was unknown but that SEAC at that time used an estimate of 1 in 4000; current DoH risk reduction strategies were of uncertain efficacy or necessity; our test could in principle be developed for accurate prevalence estimation to guide risk estimation and risk management potentially including routine blood screening if then deemed necessary and testing of at-risk populations (several thousand recipients of implicated blood or blood products or contaminated surgical instruments had already been notified of their risk status by HPA). I reminded him that the Unit had been funded by MRC (in the light of the recognition of cases of secondary vCJD related to blood transfusion) to develop a therapeutic anti-PrP monoclonal antibody with the eventual aim not only of treating clinical prion disease but also to be able to treat such healthy at-risk individuals (post-exposure prophylaxis) with the aim of curing the early infection prior to the infection entering the brain (neuroinvasion) and thereby preventing progression to the fatal clinical disease. I explained that the essential next step was anonymous testing of 5000 healthy US donors (assumed to have negligible exposure to BSE) to estimate the false positive rate. This had followed discussion with Dr Marc Turner (Medical Director Scottish Blood Service and Chair of the Prion Working Group (PWG) of the National Blood Service) at the request of DoH. He kindly arranged contact with the American Red Cross about provision of samples for testing. The prototype test was labour intensive and I conveyed our estimate that to analyse 5000 samples in less than 12 months would require we recruit several additional full-time technicians. The criterion set by an EU vCJD blood test technical specification required >99.5% specificity. DoH advised we approach MRC for funding this stage. Were the test specificity met on the 5000 samples, the next stage would be to screen a very large number (20,000) of UK samples under guidance from the PWG to obtain an estimate of UK prevalence of detectable prionaemia. This would require either a large number of trained technicians or a significant improvement in test throughput to achieve in a timely fashion.

We had for some time been actively seeking a commercial partner expert in blood diagnostics and these efforts continued. We are an academic lab with expertise in the basic science and in handling and assaying human prions, but not in subsequent test development needed to convert the laboratory prototype into a robust high-throughput assay the Blood Service could routinely use. In addition, leaving aside our lack of relevant expertise, any work in test optimisation and to increase throughput

we did attempt ourselves in the interim was likely to become redundant as commercial diagnostics companies have proprietary technologies and platforms and would inevitably adapt our prototype to their systems. Colleagues at the National Blood Service and HPA were very supportive but lacked the resources to conduct this work. We were unable to attract a commercial company and this aspect is covered in answer to question 18 below. Given the public health considerations, we did therefore try our best to find a way forward ourselves but clearly this would require additional funding and technical staff.

Use of our test for diagnostic purposes as service evaluation in samples from patients referred with suspected vCJD was given governance approval from UCLH NHS Trust R&D and the Clinical Director of the National Hospital for Neurology and Neurosurgery in February 2011. We asked the Association of British Neurologists to circulate a note in their newsletter to UK neurologists "Availability of a blood test for variant Creutzfeldt-Jakob disease at the MRC Prion Unit, Institute of Neurology, London: Further to a review at University College London Hospitals NHS Trust, we are now ready to offer our blood test for diagnosis of variant Creutzfeldt-Jakob disease on the basis of an NHS service evaluation. Patients with suspected prion disease are eligible for the assay, but we are not offering this for healthy at-risk individuals at present. Please visit www.nationalprionclinic.org for more details about the test and how this can be obtained. Simon Mead, Peter Rudge and John Collinge."

I had further correspondence with DoH in February 2011 about the EU Common Technical Specification (CTS) for a vCJD blood test. The Unit had given our opinion to the MHRA during a consultation exercise in 2008 that given the lack of knowledge about which human blood compartments contained what proportion of infectivity, it would be inappropriate to limit a test to a defined blood component. However, we noted that the CTS now specified use of plasma, thereby excluding our test which used whole blood. We considered it likely that much, if not the majority, of infectivity would be cell-associated making plasma in any case an inappropriate choice. I wrote appealing this decision to DoH on 10th February 2011 [WITN3093006]. My understanding is that the CTS was introduced without modification. It meant that our test could not in principle meet the CTS as this stipulated use of plasma and our test was designed to work on whole blood. In addition, we felt the test sensitivity required on human samples was inappropriate given uncertainties about whether all patients with vCJD would have detectable prionaemia.

Following a meeting I had at the Unit with Dr Lorna Williamson (Medical and Research Director, NHS Blood and Transplant) and Dr Nick Watkins (UK Blood Services Prion Working Group), Professor Marc Turner wrote to Dr Mark Noterman at DoH on 18th March 2011 (copying CMO) to support testing of 5000 US blood samples and hoping that funding could be identified. He also stated that they did not see the need to distinguish between whole blood and plasma, rather that the analyte used was readily accessible from a blood donation. He stated that the UK Blood Services "continue to support the principle that both specificity and prevalence studies remain on the critical path to the implementation of vCJD screening assays for blood donors".

Having met on 17th February with Sir John Savill and Dr Rob Buckle at MRC Head Office, I received an invitation on 9th March 2011 to submit an application for funding the screening of 5000 US blood samples to MRC. This was to be peer reviewed by the MRC Strategy Board. I was informed that, if agreed, MRC would only pay 50% of the costs (as an MRC Supplementary Award) with the remainder to come by redirecting funds from my existing Unit research budget. Given the public health importance of this work and the lack of alternative support or partner to complete this work I agreed to this. An application entitled "Further development of a blood test for variant CJD prion infection: Case for MRC Supplementary award" was submitted for review and requested funding for six temporary

additional technical staff, rented laboratory space, some major equipment and laboratory consumables (due to space limitations at the time it was necessary to commission a new laboratory) to conduct the screening of 5000 US blood samples. In addition, we proposed preliminary laboratory work on developing a second type of test we had been developing (Tattum et al *Transfusion* 2010) that although itself not suitable for screening, might be used as a *confirmatory test* on those samples testing positive on screening (an important issue for the Blood Service if a version of our test or another test were developed for donor screening). The total funding requested was £525,472. We also, as MRC had requested, included a section on intellectual property (IP) arrangements and business model envisaged in moving forward. In this application, we highlighted that while potential commercial partners (see response to question 18) had expressed some interest, they considered an initial estimate of UK prevalence of vCJD prion infection based on a subsequent study using our assay to be critical to any business case. A Supplementary Award of £200,000 was made to the Unit.

On 1st April 2011, I met with the then Parliament Under Secretary for Public Health, Ann Milton MP and the CMO, Professor Dame Sally Davies at the Department of Health. I discussed progress to date, what I considered the important next steps in seeing whether our test could detect carriers and estimating the prevalence of silent infection in the UK population. I outlined the challenges of progressing these aims and the need for a commercial diagnostics company to develop our assay into a high throughput test the Blood Service might eventually use for screening donated blood. I explained that during extensive discussions with diagnostic companies (see response to question 18), they were unconvinced of a business case without seeing data on prevalence of infection in the UK population indicating there would be a market for a test which would require considerable investment on their part. The minister and CMO advised me that they were not in a position to fund further evaluation or prevalence screening. The CMO wrote to me on 8th April 2011 [WITN3093007] in a follow up to that meeting stating that the Department saw the availability of an effective decontaminant to use in the NHS on surgical instruments and an effective, both sensitive and specific, blood test for screening blood donors and potential patients as public health priorities. She confirmed that with the publication of our recent *Lancet* paper on the blood test we had now delivered on both these goals for the Department as they had asked and thanked me on behalf of the Department and the public. She advised returning to the core research programmes of the MRC Unit and emphasised that to commercialise these products "the market will have to be left to work". Unfortunately, no such commercial interest materialised (see response to question 18) and we remained concerned to progress this work in the public interest.

On 11th July 2012 on the advice of Professor Noel Gill at HPA and Professor Marc Turner in his capacity as Chair of the NBS Prion Working Group, I wrote to Professor George Griffin, Chair of the Advisory Committee on Dangerous Pathogens (ACDP), to seek their view on undertaking a vCJD blood prevalence study [WITN3093008]. I noted that at that time we had completed testing of 3500 of the 5000 US samples and all were negative, consistent with a very low false positive rate. He replied by letter on 2nd October and requested structured information on our test's methodology and performance which we provided [WITN3093009].

Results from analysis of archived surgical appendix samples for disease-associated PrP by the Health Protection Agency (HPA) were released in August 2012 and gave a higher estimate of 1 in 2000 positive (Gill et al *BMJ* 2013 – PRIU0000069).

Our MRC funded screen of 5000 US donor samples and further evaluation of test performance was completed by December 2012. 0/5000 samples were positive, consistent with the very high test specific necessary for a screening test and making a follow-on prevalence study feasible. That 0/5000 US samples tested negative was consistent with 100% test specificity (95% confidence intervals 99.9-

100%). The full test performance data together with data supporting its use in neurological diagnosis were subsequently published in the leading peer reviewed journals *Blood* and *JAMA Neurology*. We concluded that the prototype vCJD assay had sufficient performance to carry out a prevalence study comparing prion-exposed and prion-unexposed populations (i.e. UK and US), and statistical power calculations indicated this would require 20,000 samples from each cohort. This feasibility study was also published (Jackson et al *JAMA Neurology*) [WITN3093010]. We considered a blood prevalence study would provide essential information for deciding if routine vCJD screening is needed for blood, tissue and organ donations and for patients before high-risk surgical procedures.

Subsequent to further discussions with MRC Head Office, we were invited to submit an outline application to progress the vCJD blood test studies. This was submitted to MRC on 20th September 2012. On the advice of MRC, I investigated the feasibility of using UK Biobank samples rather than UK blood donors since DoH had taken a decision that blood donors testing positive would have to be notified, precluding an anonymous study design. I contacted Professor Sir Rory Collins, Director of UK Biobank, to investigate if Biobank were able and willing to provide 20,000 samples from UK individuals proposed for a UK prevalence study. He wrote a letter of support on 23rd November 2012 to confirm that this was indeed possible. He noted that "UK Biobank participants have agreed to their data and samples being used for any kind of health research which is in the public interest (which, clearly, is the case for your proposed study), and for linkage to all types of medical and other health-related records on the understanding that there will be no feedback of any individual results. Consequently, the UK Biobank resource would seem to be ideally suited for conducting your project rapidly and cost-effectively and we would be delighted to facilitate it in any way we can." [WITN3093011]

We were invited by MRC to submit a full application for peer review which we did on 13th December 2012. The total estimated cost over three years was of £1,264,529. This was sent to 10 external referees for peer review to be followed by a funding decision by MRC Strategy Board. We were sent written peer review reports from the nine of the ten external experts who had responded. There was a broad assessment of the MRC Prion Unit as world leading in this area and with a single exception all reviewers scored our proposal as Very High Quality, Excellent or Exceptional. We were invited to respond to the referee's comments prior to the Board decision and did so in detail. In particular, we noted that the main concern of the single reviewer who had given a low score was that we should have first demonstrated that the test can detect pre-symptomatic vCJD cases by study of such cases. The reviewer was unaware that there were no such samples available for us to test; indeed that was the rationale for doing the comparative study of 20,000 US and UK samples. There was no other test that could identify such healthy but vCJD prion-infected individuals. In addition, I understand that MRC sought opinions from a number of public health bodies and Department of Health officials but we did not see or have the opportunity to respond to those reviews. In later correspondence on 4th March 2013, Dr Catherine Elliot at MRC asked if the Unit could contribute funds from our core budget to support the project were it to be supported by MRC Strategy Board. I explained that this was not feasible and that indeed my Business Director had previously been specifically told by MRC Finance not to include any funding of this project in our Unit budget submission [WITN3093012].

We received the decision of the MRC Strategy Board by email from Dr Catherine Elliot on 13th March 2013 which was a rejection of our application. A brief summary of the reasons for this were given. The Board recognised the high quality of the science but thought that "the parameters of the current test, and in particular the sensitivity, were such that is was not good enough for adoption as a valid screening tool" and the Board "had secondary concerns about the use of the UK Biobank cohort in relation to the generalisability to the wider UK population and the major ethical issues relating to feedback". They further noted that "DH and BTS have a strong position that, for public health reasons,

positive test results must be fed back if the individual can be identified..". They recommended "that further development must first improve the sensitivity of the test" and stated that such research should be supported by the Unit's existing core funding [WITN3093013]. We disagreed strongly with the scientific and ethical reasons given for their decision. Although there was no process to appeal an MRC Board decision, I nevertheless wrote to Dr Elliott on 17th April 2013 to challenge this decision (document PRIU000074). This document gives our detailed rebuttal on the issue of test parameters and use of Biobank samples and so I will not repeat that here. However, as I noted in my appeal letter, the fact that an MRC Board had turned down an application (from an MRC Unit) not due to funding limitations, but on scientific and ethical grounds (despite our firmly disputing both), made it extremely difficult to seek funding for this work elsewhere.

Dr Elliott responded to my letter on 8th May 2013 repeating the opinion of the Strategy Board. She proposed (1) MRC have further discussion with the ACDP and (2) asked me to provide further information on the additional data a potential commercial partner would require [WITN3093014]. I do not know what transpired from (1) and was perplexed by (2) as the rejected application was precisely aimed at providing those further data, as the application explained in detail. I had a final exchange of emails with Sir John Savill, the MRC CEO, on progressing the blood test on 16th October 2013 where I reiterated that I felt the Board had misunderstood that the test sensitivity they described as "only 71%" in no way prevented the proposed study (comparing a large UK and US population sample) determining whether the prototype test could detect carriers and getting a "snapshot" of prevalence of prionaemia in the UK - the key data required to have any hope of a commercial company investing in the necessary assay development to produce a practical high-throughput test for the Blood Service [WITN3093015].

As the Inquiry is aware, there was further discussion on progressing research on our prototype blood test at the House of Commons Science and Technology Select Committee Inquiry into vCJD and blood safety and this was covered in their report: "After the storm? UK blood safety and the risk of variant Creutzfeldt-Jakob disease" published in 2014 ( TSTC0000052 ).

By 2015, with the lack of progress in our grant applications and commercial development of the test, I had the impression that there was no appetite for development of our prototype test. I took the opportunity while at a meeting of Senior Investigators of the Faculty of the National Institute for Health Research (NIHR) in 2015 or 2016 that I and the then CMO, Professor Dame Sally Davies, were both attending, to speak to her informally. I was able to catch her only very briefly and she reiterated her earlier advice to now focus on other areas of research.

Following discussions with colleagues, it came to my attention around December 2015/January 2016 that a number of blood samples from blood donors who subsequently developed vCJD (including from donors where recipients of their blood had gone on to develop vCJD) were in fact available in blood transfusion service archives in England and Scotland. I understand that these samples had been collected and documented as part of a study called the Transfusion Medicine Epidemiology Review (TMER). The TMER is a collaborative project between the National CJD Research & Surveillance Unit (NCJDRSU) in Edinburgh and the UK Blood Services "to investigate whether there is any evidence that Creutzfeldt-Jakob disease (CJD) or variant Creutzfeldt-Jakob disease (vCJD) may have been transmitted via the blood supply". As explained above, our planned comparative study of 20,000 US vs UK donor samples was considered necessary to try to assess if the test could detect asymptomatic but infected donors precisely because no samples from donors known to have died of vCJD were available to address this question directly. Had we been aware of, and been given access to, such samples they could have been rapidly tested using our prototype vCJD blood test (assuming these

samples were suitable for our test). Indeed, such work could have been carried out in a few days at the MRC Prion Unit and would not have required any new funding.

I have recently seen some email correspondence dating back to 2006 between officials at the National Blood Service and Department of Health (including a DoH official I understand was involved in commenting on our subsequent MRC grant application) regarding these samples and also a list of archived samples dating from 2008. This correspondence regarding "the availability of archive samples from vCJD transmitters/donors who later developed vCJD" was discussed at a meeting of the ACDP TSE sub-group in January 2016 (PHEN0002460_001) and was circulated to officials from MRC, DH, DEFRA, PHE, FSA, devolved administrations as well as blood transfusion services. It is not clear why my Unit was not informed of the existence of such samples, at least in 2011 on publication of our prototype test in the *Lancet*, or during subsequent meetings with officials to discuss our prototype test and subsequent funding applications. This is discussed further in response to question 19 below as it transpired from subsequent inquiry that these samples were unlikely to be suitable for testing using the prototype test we had developed in the absence of knowledge of such samples.

18. **Which commercial partners did you approach to fund further evaluation and prevalence screening for the blood test you had developed (PRIU0000084)? Why, in your view, was a commercial partner not found?**

A number of commercial partners were approached by colleagues at D-Gen with assistance from MRC Technology and the then Deputy Chief Executive of the MRC, Mr John Jeans. These included Abbott Laboratories, The Binding Site, DiaSorin SpA, Ortho-Clinical Diagnostics, Novartis and Siemens. I also spoke to Professor Sir John Bell who was then on the Board of Roche. In my view the reason a commercial partner was not found was uncertainty as to the business case to justify the significant investment that would be required to convert our prototype test into a robust high-throughput test on their proprietary platforms. As explained above, we did not know whether our prototype test was able to detect carriers of vCJD prion infection or have data on the prevalence of prionaemia in the UK blood donor population.

19. **What research has been conducted or proposed for the blood test since the Parliamentary Inquiry in 2013?**

Firstly, we published a number of scientific papers of relevance. These include a case report of a patient with vCJD who had extremely low levels of lymphoreticular disposition of prion protein (Meadet al, *JAMA Neurology* 2014 - NCRU0000197_002). This suggested that some patients with vCJD have very low levels of prions outside the central nervous system and may not have detectable prions in blood. This had implications for estimates of the sensitivity of a blood test and supported our view that our reported test sensitivity of "only" 71% may indeed reflect the fact that some cases did not have prionaemia and that our test may be detecting nearly all that do. We also published a study on the diagnostic accuracy of the DDA and the feasibility of using our test for population screening for vCJD in 2014 (Jackson et al, *JAMA Neurology* 2014, WITN3093010 and letter – PRIU0000231). We concluded that the assay's established high sensitivity and extremely high specificity supported using the assay to screen for vCJD infection in prion-exposed populations and its clinical use in patient diagnosis. RJIRJ The Parliamentary Inquiry published its report in July 2014 [WITN3733002]. They

considered that a vCJD prevalence study utilising a version of the prototype test we had developed would be of considerable value and recommended "that the Government ensures that a large-scale vCJD blood prevalence study be initiated in the UK within the next 12 months". On reading the report I wrote to Sir John Savill, MRC CEO and pointed out the Inquiry's recommendation regarding the prevalence study that MRC had declined to fund. He replied to say that he thought the report "firmly puts the ball in the Department of Health's court" and suggested "quietly waiting to see how Government responds" [WITN3093016].

I wrote to the CMO Professor Dame Sally Davies on 30th December 2014 noting the recommendation of the House of Commons Science and Technology Select Committee report to DoH to conduct the prevalence study we had been proposing since 2011 but which had not been funded [WITN3093017]. I noted that wehad met with colleagues from Public Health England (Professor Noel Gill and Dr Sinka), NHS Blood and Transplant (Dr Lorna Williamson) and Professor Marc Turner (Medical Director SNBTS and Chair Prion Working Group) to discuss the report, the subsequent meetings of the ACDP TSE subgroup, and the correspondence between its Chair, Dr Roland Salmon and herself and that we had explored possible ways forward but that there was no funding for a prevalence study. I reminded her that she had previously advised in 2011 that after developing the prototype test we should return to our fundamental research and that further development should be handed to industry. I explained that this had been tried by D-Gen Limited (the academic spinout company to which the test intellectual property had been assigned by MRC) and MRC Technology but without success and again that the feedback received was that before a commercial investment could be contemplated an industrial partner would need to be satisfied that our assay could both detect asymptomatic carriers and that a test would be likely to be adopted for large-scale screening of donor blood – both of which would be clarified by the results of a prevalence study. We therefore remained in a "Catch-22" situation. I explained that I felt the Unit had taken things as far as we could but reiterated the concerns of myself and my Unit colleagues at the ongoing unquantified risks of iatrogenic transmission of blood-borne prions. I suggested that if the statutory bodies and agencies with public health responsibilities in this area wished to pursue a UK blood prevalence study using this technology in the future they should therefore now liaise directly with D-Gen and referred her to its Chairman, Mr Bernard Jolles. I explained however that the Unit would continue to be available to assist with any technical matters or advice if required. Dame Sally replied on 20th January 2015 thanking me for my letter and saying that she would ensure that those with an interest in further development were referred to Mr Jolles [WITN3093018].

Dr Lorna Williamson (NHSBT) and Dr Philip Minor (NIBSC) wrote to Mr Jolles in March 2015 to propose a draft protocol for further work on the DDA to be carried out by one of their scientists (Dr Gary Mallinson) at NHSBT Filton supported by seven months of funding that was available only from March to September 2015 [WITN3093019]. This proposal argued that the only practical way to determine whether the DDA could detect asymptomatic infections was to test blood samples from animal models of prion disease. It proposed transfer of the test methodology to NHSBS Filton followed by an extensive series of investigations by Dr Mallinson including whether the assay was able to detect pre-clinical infectionfrom two different animal models (from primates and sheep) and work to try to produce a higher throughput version of the assay. The work programme was completely unrealistic in terms oftimescale. Mr Jolles discussed these proposals with me and responded on 13th May 2015 with the view that while having an independent evaluation of the assay performance was certainly of value, there was no point in conducting the animal sample testing as the assay would have to be re-optimisedfor each species, a lengthy and uncertain process, and performance in that species would not necessarily indicate similar performance in human samples due to differences between prion strains, blood composition and immune systems [WITN3093020]. To determine whether the assay could detect human carriers, human samples would have to be tested. He reiterated the Unit's

view, which had been supported by the Parliamentary Inquiry, that the key next step was the comparison of UK and US donor samples using the existing assay format. He pointed out that while the current assay was laborious, the MRC Unit had conducted a screen of 5000 US samples already using the DDA and produced a fully worked up and costed practical proposal to scale that up to screen 20,000 UK and US donors. Indeed, the Unit's proposal had been to contract a respected commercial laboratory to conduct the laborious screening work. Work to increase the throughput would be challenging and time consuming and simply delay the proposed prevalence study. Mr Jolles proposed a meeting of relevantparties to discuss these issues further.

Further work was being completed at the MRC Prion Unit during this period including pilot studies to see if our in-house Unit robotic platform could be used to increase test throughput and reduce costs of a prevalence study. Results were not encouraging and it was not considered sensible to pursue further given that the proposed prevalence study could be readily conducted with the existing published assay and cognisant that a major diagnostics company that undertook to develop a high throughput test for practical blood donor screening would adapt our assay to their own proprietary assay platform making such academic pre-development work redundant. In addition, in the course of on-going work in the MRC Prion Unit to study "biomarkers" of disease during the incubation period of prion infection in a mouse model, we were also able to show in fact that the DDA was able to detect samples taken during the incubation period prior to clinical onset. As stated above, these data could not be taken as indicative that this would translate to human carriers but was nevertheless encouraging and provided a "proof of principle" which further negated any need for the further proposed animal studies (in sheep and monkeys). These data were shared with the ACDP TSE Group and subsequently published (Sawyer et al, Preclinical detection of infectivity and disease-specific PrP in blood throughout the incubation period of prion disease *Scientific Reports* 2015) [WITN3093021].

There was further discussion and correspondence between Mr Jolles and colleagues at NHSBT, Marc Turner at SBTS, Chair of ACDP TSE Sub Group Roland Salmon during 2015 [WITN3093022]. Mr Jolles noted the mouse model studies from the Unit and reiterated D-Gen's willingness to approve transfer of the assayto an independent laboratory to determine directly whether it could detect human carriers via a comparative study of UK and US donors (noting that the design and statistical basis for such a studyhad now been published in the peer reviewed journal *JAMA Neurology*) [WITN3093010]. In July 2015 he wrote further to Dr Salmon seeking to progress matters and proposed a meeting to discuss: 1. Assay throughput; 2. Design of a prevalence study; 3. The laboratories and individuals to be involved in the study; 4. The process for giving approval for such a study; 5. A timetable for the individual steps in the process. I understand that Mr Jolles also asked that members of the ACDP Subcommittee declare any conflictsof interest since he was concerned that several worked in the field and may be involved in development of alternate tests. During these discussions, it emerged in late 2015/early 2016 that blood samples from blood donors who had subsequently developed vCJD were available and stored at NHSBT or SBTS laboratories (as also discussed above in response to question 17). Further correspondence took place as to the availability of such samples and their suitability for analysis using the DDA as this had the potential to provide immediate direct evidence that the DDA could detect asymptomatic human carriers. Mr Bernard Jolles from D-Gen corresponded with Roland Salmon, chair of ACDP TSE Sub-committee, Dr Patricia Hewitt and Professor Marc Turner from NBS and SBTS about availability and provenance of these samples in 2016 and it was concluded none were suitable for analysis by the DDA as it was reported that the only available samples were plasma and serum, not whole blood as used in the DDA.

Mr Jolles attended an ACDP TSE Sub-Group meeting on 29th September 2016 together with my Unit colleague Dr Graham Jackson who took questions on his data on the mouse model. I am not aware that any further progress was made (PHEN0002461).

Fundamental research studies on molecular diagnostic strategies in prion disease were led in the Unit by Dr Jackson. At the Unit's quinquennial review by MRC in 2014/15, Dr Jackson's future research proposals (which aimed: 1. To gain a molecular description of amyloidogenesis and prion replication *in vitro* and 2. To achieve the quantitative detection of abnormal PrP in the blood, CSF and urine of CJD patients) were not supported and he lost his research team. I appealed this decision and he was permitted to apply for a subsequent MRC Supplementary Award on diagnostics research. He submitted an application: "Development of enhanced methods for the detection of prion infection and disease" which included studies to address the earlier criticism of the MRC Strategy Board in response to our prevalence study application that the sensitivity of our prototype blood test should be improved. This application was also rejected.

In September 2016, DoH unexpectedly announced a call for applications for research to address policy issues in vCJD under their Policy Research Programme (PRP). Despite the preceding several years of unsuccessful attempts to progress the comparative study of UK and US blood samples, we decided to have a further attempt to fund such a study given this was a specific call for applications from DoH, the continued public health uncertainties, and the clinical utility a test to detect the carrier state may have for at-risk individuals exposed to contaminated blood and blood products. Dr Jackson prepared an application entitled: "Comparative study of UK and US blood samples to determine if asymptomatic carriers are detected using a prototype test". This was submitted as a "Stage 1" outline application for review. If successful, a full "stage 2" application would be requested. Unfortunately, we heard on 12th December 2016 that following review by the PRP's Commissioning Panel our application was not to be considered further [WITN3093023]. No external expert peer review appears to have been sought and only the briefest of feedback was received. The Panel agreed that the proposal addressed an important policy priority, but felt that pre-clinical (unspecified but presumably animal model) work to validate the DDA test was necessary before proceeding and that there were (again unspecified) concerns about lack of detail regarding US human blood samples. There were also (unspecified) concerns about our public communications strategy. It was stated that it was not possible to provide more detailed individualised feedback.

20. **What is your current view with regards to the likelihood and benefits or disadvantages of implementing donor screening for vCJD?**

In my view, the case for donor screening for vCJD prion infection following the recognition of widespread lymphoreticular involvement in vCJD in 1997 was clear and accentuated by the subsequent recognition of secondary vCJD related to use of blood and blood products in the 2000's and the anonymised screens of appendix tissues by PHE with estimates that 1 in 2000 of the UK population may be infected in 2013. However, it has been extremely reassuring that no cases of vCJD have been detected related to blood transfusions carried out since universal leukodepletion of donor blood. This suggested that leukodepletion has been highly effective in reducing the risk of iatrogenic transmission of vCJD prions by blood transfusion. As a neurologist who has been very involved in the diagnosis and management of patients with vCJD I would want to do everything possible to eliminate any further risk of secondary vCJD. However, weighing up the benefits vs disadvantages and costs of introduction of this or other risk reduction measures is a matter for health economists who properly

advise policymakers at the DHSC. Given that no cases of vCJD have been identified in the UK since 2015 and the last case associated with use of blood or products was recognised in 2007, donor screening at this stage is most unlikely to be considered cost-effective. I would however note the caveats that: (1) cases of identified sporadic or "classical" CJD continue to rise and we cannot currently exclude whether a fraction of such cases represent BSE-related infections manifesting as classical CJD; (2) the finding of 1 in 2000 positives in the PHE appendix study remains of uncertain significance. Further development of a donor screening test may be helpful in resolving this uncertainty and, should such a test be shown to detect carriers, could potentially be used clinically to advise those at risk (potentially offering emerging therapy as secondary prophylaxis in those testing positive) as well as aiding differential diagnosis of suspected vCJD patients (see below).

21. **The Inquiry is aware that a prototype test for vCJD is available through the National Prion Clinic. This test is advertised on the NHS' website, please visit: https://www.nhs.uk/conditions/creutzfeldt-jakob-diseasecjd/diagnosis/**

    a. **Is this the same test you developed in 2011?**

Yes, the Direct Detection Assay (DDA) as published in *Lancet*.

    b. **How would a patient obtain access to the test? Please outline any procedural tests/thresholds required for this test to be given to a patient.**

This would follow discussion or referral of a patient with neurological disease in whom vCJD was suspected by the referring clinician (usually a consultant neurologist or a member of their team) to the National Prion Clinic. The DDA would be conducted if considered appropriate to aid diagnosis.

    c. **Is this test being used on a routine basis? If not, why not and when is it likely to become routine?**

The test was being carried out by expert staff of the MRC Prion Unit Diagnostics Research Programme. However, as explained above, the funding of this programme was discontinued by MRC and the trained technical staff were lost. Clinical requests for DDA are now very infrequent in any case given the rarity of vCJD. The senior scientist who developed the prototype test is still at the Unit and can perform DDA if required but this is not now routinely available.

22. **Please answer the following in so far as you are able:**

    a. **Are pre-surgery patients and/or blood donors routinely asked about their vCJD notification status? If yes, when was this measure adopted?**

My understanding is that this was instituted for pre-surgery patients from 1998 and guidance has been updated by DHSC in a number of documents over the subsequent years. Formal guidance is given in: "Assessment to be carried out before surgery and/or endoscopy to identify patients with, or at increased risk of, CJD or vCJD" Annex J, first published in 2006 [WITN3093024] (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/636811/Annex_J_presurgical_assessment_vCJD.pdf). We carried out a small research study at the National Prion Clinic, based on anecdotal concerns such questioning was not being uniformly applied, and drafted and trialled a simple questionnaire for that purpose to assist colleagues. We published this in the *Journal of Hospital Infection* in 2005. I am unsure about current practice at blood donation centres but I understood that such screening questions are asked. The DHSC and National Blood Service would be best placed to give relevant dates and details.

b. **Has the 2021 vCJD update, re-introducing the use of UK Plasma, had any effect on the questions asked of pre-surgery patients and/or blood donors?**

Not so far as I am aware. Annex J referenced above was last updated in 2017. However, DHSC or NBS would be best placed to answer this.

**Section 5: Notification and Clinical Care of Persons at Risk**

23. **The Inquiry is aware you were briefly associated with the CJD Incidents Panel, before resigning in 2000 (NHBT0008546). With this in mind, please describe any role you played with the notification process as part of the CJD Incidents Panel or in another capacity.**

My principal role here was as an NHS clinician seeing patients referred with suspected prion diseases. I had established a specialist clinic at St. Mary's Hospital in London around 1997 which was subsequently designated the National Prion Clinic and relocated to the National Hospital for Neurology and Neurosurgery in 2001. We provide a national service and liaise closely with the NCJDRSU to ensure both Units are aware of all suspected cases. In all patients we would inquire about history of previous surgery, blood transfusion, treatment with blood products or pituitary hormones and whether they were ever a blood donor. We would always take a family history to investigate whether their condition could relate to a prion gene mutation and with appropriate consent, perform genetic testing to confirm or exclude such a mutation. All patients with, or at risk of, developing prion disease would be counselled about infection control, in particular that they should not be blood or organ donors and should inform surgeons (including dentists) of their status prior to any procedure. Where an inherited prion disease mutation was identified we would encourage this guidance to be shared with other family members and offer counselling to at-risk family members. Where there was any suggestion of an incident – for example recent relevant surgery or blood donation from a patient with prion disease – there would be notification of the relevant Consultant in Communicable Disease Control. Potential incidents involving blood donation would generally be handled by the NCJDRSU who liaised closely with the NBS. The CJD Incidents Panel was established in 2000 to advise on actions that needed to be taken after such an incident.

24. **Were the notification exercises effective in your view? If not, what could and should have been done differently?**

I will address this together with your question 25 below.

25. **In letters dated January 2006 you indicated that patients exposed to vCJD through blood transfusion "had not been offered access to best practice care in the NHS" (DHSC0004223_065; DHSC0004223_066). Please elaborate on what you meant by this and the reasons for your view, and any subsequent actions taken by the Department of Health (DHSC0004223_067).**

My colleagues and I at the National Prion Clinic were concerned that the small cohort of individuals exposed to blood transfusions from single vCJD infected donors were at relatively high risk and we wanted to ensure that they had access to early specialist care and support should they wish. We felt that such individuals should be made aware of our specialist service and the PRION-1 therapeutic trial (which had been established at the request of the Department of Health) via their General Practitioners. vCJD is not only a rare condition (that very few GP's will have encountered) but its initial clinical features (for example anxiety, depression and tingling in the legs) are commonly seen in the general population making early diagnosis challenging. In this "at-risk group", there was a significant risk that vCJD might develop and access to specialist monitoring to such individuals, should they wish it, could allow early diagnosis and access to clinical trials. My further letter to Sir Liam Donaldson on 26th January 2006 (DHSC004223_066) indeed highlighted a patient we had seen with blood transfusion-associated iatrogenic CJD who had been symptomatic for around a year prior to referral, exemplifying my earlier concerns. Dr David Harper, Director of Health Protection, replied on behalf of Sir Liam (DHSC0004223_067) stating the Department's view was that relevant GP's had been notified of the availability of specialist centres and encouraged to refer where appropriate. Dr Harper also said that as some time had passed since the HPA had made contact with the GP's, an independent group would be set up to review current arrangements and make recommendations for follow up care. This led to the formation of the vCJD Clinical Governance Advisory Group (vCJD CGAG).

With respect to question 24, I am not in a position to comment how effective the HPA notifications were overall. I did have direct clinical experience via the NPC of a number of individuals from this risk group and had feedback that several did not feel well supported. For example, one person from the at-risk group who was referred to the NPC (on whom I made a domiciliary visit as she was too anxious to travel to London) had a history of mental illness and informed me that she had been notified of her risk of developing vCJD by a letter that had arrived on Christmas Eve. I think it would have been preferable if the NPC had been permitted to assist our busy GP colleagues with specialist clinical and counselling support more proactively. This is no criticism of colleagues but NHS services are not always perfectly co-ordinated and may be overstretched and it does make sense to make best use of specialist teams ready and able to provide timely support. I gave further examples of my concerns to the vCJD CGAG as part of a detailed presentation of our clinical service and research work on 16th June 2006 [WITN3093025].

26. **You are acknowledged as contributing to the work of the vCJD Clinical Governance Advisory Group (HCDO0000902, page 4). In your view, was the clinical care advice offered by this group for persons at risk of vCJD effective?**

In my view, the Group carefully considered the relevant issues, consulted widely and produced a clear and helpful report. They recognised the need for the at-risk group to be given good care and sensitive support at all times. Their recommendation was for a partnership between GP, local consultant neurologist and specialist centres. We certainly concurred with that approach (which was indeed our usual practice and would generally be the case with rare diseases) and their other recommendations. However, it is difficult to comment on whether their advice was effective in optimising care and support for the at-risk group as only a minority were subsequently referred to the NPC.

**Section 6: Prevalence**

27. **What is the prevalence of vCJD in the general population? In responding to this you may attach any notable research studies or papers, reports, recommendations, look back exercises and databases which have addressed this issue. Please describe the extent of your involvement with these studies and developments**.

No patients have been diagnosed with vCJD for several years. I assume this question refers to the prevalence of clinically silent vCJD prion infection, rather than the disease vCJD, in the UK population.

My laboratory demonstrated in 1996 that vCJD was caused by the same prion strain as that causing epidemic BSE in cattle (Collinge et al *Nature* 1996) (MHRA0021347) and the extent of infection in the community following the widespread food borne exposure to BSE prions was unknown. In January 1997 we reported our finding of deposition of disease associated PrP in tonsil tissue in vCJD patients (Hill et al *Lancet* 1997) (DHSC0004747_040); subsequent studies showed the utility of tonsil biopsy to diagnose vCJD and the wide involvement of other lymphoreticular (LRS) tissues in vCJD (Hill et al *Lancet* 1999; Wadsworth et al *Lancet* 2001). The original finding in tonsil led me to suggest to the Department of Health that tonsils removed during routine surgery could in principle be collected and analysed anonymously for the presence of disease-related PrP and might provide an initial estimate of the extent of vCJD prion infection in the population. A committee was established by DoH to discuss the ethics and design of such studies and several studies were commissioned and performed. We were funded by DoH to perform one of these studies and screened 2000 consecutive tonsillectomies using two methods: immunoblotting to detect PK- resistant PrP and immunohistochemistry to detect the characteristic deposition of disease-related PrP in association with follicular dendritic cells. We found no positives but while highly laborious this was arelatively small study (Frosh et al *Lancet* 2004) (RLIT0000727) as was a parallel study in both tonsil and appendix tissueby colleagues in Edinburgh and Plymouth (Hilton et al *Journal of Pathology* 2004) (NHBT0063957_002). Larger scale studies were thought essential and subsequent screening of LRS tissues has been performed using appendixtissue since large archival collections of appendicectomy samples were available in hospital pathology departments. These samples were formalin-fixed and so only immunohistochemistry to detect abnormal

PrP immunostaining of follicles was possible. Several such studies have been performed by Public Health England (PHE). I was not directly involved in these but members of my Unit staff assisted with genotyping and immunohistochemistry and some were co-authors on subsequent publications. The first PHE study reported three positives from 12674 samples giving a prevalence estimate of 237 per million or around 1 in 4000. A second larger study reported 16 positives from 32441 samples (prevalence estimate of 493 per million or around 1 in 2000) (Gill et al *BMJ* 2013) (PRIU0000069). Such estimates were clearly worrying despite the falling number of clinical vCJD cases since it was known that human prion incubation periods could span decades. Indeed, we had shown by study of the kuru epidemic in Papua New Guinea that incubation periods following oral exposure could exceed 50 years (Collinge et al, *Lancet* 2006) [WITN3093026]. My Unit had also reported the phenomenon of subclinical prion infection where laboratory mice could be infected with prions from another species and live to old age without showing signs of disease despite harbouring high levels of prions in their brains (Hill et al *Proceedings of the National Academy of Sciences* 2000) (DHSC0004808_059). This phenomenon has since been described by multiple other laboratories. Assuming the positives detected by the PHE were true positives reporting authentic vCJD prion infection, it was not possible to determine whether such individuals had preclinical infections (and would eventually develop the disease if they lived long enough to complete the incubation period) or subclinical infections (and would not themselves ever develop the disease). Such subclinical infections (as with preclinical infections) would nevertheless be expected to pose a risk of infecting others if they became blood or organ donors for example. Research in laboratory mice had shown that tissue from subclinically infected mice (that live a normal lifespan without developing disease) produce a lethal infection in other mice following inoculation.

However, interpretation of the PHE findings now is increasingly hard to correlate with the absence of clinical vCJD cases. A problem with interpreting these data is that no control group of appendix samples from a country with minimal or no BSE exposure was carried out. I recall there being discussion of a comparative study with Canada but so far as I am aware this was not performed. Finding similar numbers of positives in such a population would suggest that the UK findings were either false positives or that a low level of LRS prion infection is seen in the normal population and does not generally cause clinical disease.

In an attempt to resolve these uncertainties a third large scale appendix screen was carried out by PHE to measure the prevalence of abnormal PrP in UK population groups thought to have been unexposed to BSE. They screened 29,516 samples from appendices removed between 1962 and 1979, and from those born after 1996 and operated on from 2000 to 2014. Seven positives were found of which two were from the presumed pre-BSE-exposure era (pre-1980) and five from the post BSE-exposure period. None of the seven positive samples were from appendices removed before 1977, or in patients born after 2000. The authors proposed two interpretations: either there is a low background prevalence of abnormal PrP in human LRS tissues that may not progress to vCJD; or alternatively, all positive specimens are attributable to BSE exposure, a finding that would necessitate human exposure having begun in the late 1970s and continuing through the late 1990s (Gill et al *Acta Neuropathologica* 2020) (RLIT0000725). Clearly, a large-scale screen of LRS tissues from a population not exposed to BSE would be helpful in further interpreting these data. It is also unfortunate that a large-scale study of blood samples as discussed above is not available for comparison, not least as it is blood that is the main concern with respect to iatrogenic transmission. However, again the lack of clinical primary or secondary vCJD casesis encouraging and does not appear consistent with the appendix results being a reliable guide to iatrogenic risk. A caveat already mentioned is the apparent increase in classical CJD cases reported in the UK and the possibility a fraction of these could be alternate forms of BSE prion infection presenting as sporadic CJD rather than vCJD and not now detected at autopsy due to the low current post-mortem rate. However, it should be noted that an apparent increase in sporadic CJD incidence is also noted in

some other countries with similar surveillance systems suggesting this apparent increase may be largely due to better case ascertainment.

28. **What involvement did the Health Protection Agency (HPA) have with the tonsil and appendix prevalence studies?**

All these studies were led by the HPA with the exception of the two relatively small initial studies as described above.

29. **What is your current view on how the prevalence of vCJD in the general population might translate into risk to the blood supply?**

The uncertainties in this regard are addressed above. Estimation of prevalence of disease-associated PrP in UK blood donors is best addressed by studies on blood.

The absence of secondary blood-transfusion associated vCJD in individuals transfused after the introduction of universal leukodepletion suggests this measure was highly effective in risk reduction.

30. **If you have an opinion, do you think that vCJD should be a notifiable disease considering the prevalence in the UK? What are the advantages and disadvantages of this?**

There is a logical case for vCJD and other prion diseases being notifiable to public health authorities; these fatal diseases are potentially transmissible by medical and surgical procedures and it is important that appropriate infection control procedures are employed where appropriate. However, when this has been raised previously, colleagues at the NCJDRSU (who are responsible for epidemiological surveillance and reporting case numbers to DHSC) have argued that making CJD notifiable may in fact paradoxically reduce reporting of the disease and that having an effective active surveillance system achieves better overall case ascertainment. Their arguments and evidence in that regard were persuasive. Additionally, for rare diseases with unusual characteristics it may be best to have specialist centres involved who are familiar with all the issues and best placed to advise and counsel patients, families and involved health professionals as necessary.

31. **In order to monitor vCJD in other countries, post mortems of those with symptoms are compulsory. If you have an opinion, do you consider that post mortems should be compulsory for those who have symptoms or are at risk of vCJD in the UK? What are the advantages and disadvantages of this?**

Post mortems continue to be important for definitive confirmation of some forms of prion disease, including vCJD. Indeed, we know it can sometimes be difficult to differentiate vCJD and sporadic CJD in the clinic and we have reported in the medical literature a patient with vCJD who would have been classified as sporadic CJD on established criteria without the post-mortem examination (Mok et al *New England Journal of Medicine* 2017) [WITN3093027]. We have also argued, based on work from studies in genetically modified laboratory mice, that BSE prion-infection of humans may manifest in different ways to that of typical vCJD, including clinical forms indistinguishable from sporadic CJD. In particular, this should be considered in individuals with different genotypes at codon 129 of the prion protein gene (VV or MV) rather than the MM genotype almost always seen in vCJD. For this reason, a high autopsyrate is desirable but I do not support making post-mortems compulsory. There are many reasons whypatients and their families may decline consent and these should always be respected in my view. However, in our experience at the NPC, consent for autopsy is given in most cases and indeed manypatients and their families are keen for this to be done not only for definitive diagnosis but to contribute to research. Conducting an autopsy is expensive and during a period where the NPC had specific funding to perform autopsies for research (as part of the National Prion Monitoring Cohort study) annual autopsy rates of over 60% were routinely obtained. Currently we do not have the level of funding necessary to support that rate and autopsies are only performed, with consent, on a very small minority of patients where there are specific uncertainties about diagnosis or where obtaining tissue for research would be particularly important. Of course, HM Coroners may mandate a post-mortem examination if they consider that necessary.

**Statement of Truth**

I believe that the facts stated in this witness statement are true.

Signed GRO-C

Dated 26th April 2022

**Table of exhibits:**

| Date | Title | Exhibit no. |
|---|---|---|
| 6 Dec 2004 | Letter from Prof. Collinge & Sir Liam Donaldson to Prof Sally Davies | WITN3093003 |
| Apr 2022 | Mead et al (2022) Prion protein monoclonal antibody (PRN100) therapy for Creutzfeldt–Jakob disease: evaluation of a first-in-human treatment programme | WITN3093004 |
| 3, Dec 2010 | Letter from Professor John Collinge to Secretary of State for Health Andrew Lansley MP | WITN3093005 |
| 10 Feb 2011 | Letter from Professor John Collinge to DoH appealing decision to use plasma on advice from the CTS | WITN3093006 |
| 8 Apr 2011 | Letter from CMO Sally Davies to Professor Collinge thanking him for his work on the test | WITN3093007 |
| 11 Jul 2012 | Letter from Professor John Collinge to Professor George Griffin | WITN3093008 |
| 2 Oct 2012 | Response from Professor George Griffin to Professor John Collinge | WITN3093009 |

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| Oct 2013 | Gill (2013) Prevalent abnormal prion protein in human appendixes after bovine spongiform encephalopathy epizootic: large scale survey | PRIU0000069 |
| Apr 2014 | Jackson et al (2014) Population Screening for Variant Creutzfeldt-Jakob Disease Diagnostic Accuracy and Feasibility Study | WITN3093010 |
| Apr 2014 | Jackson et al (2014) Blood Test for Variant Creutzfeldt- Jakob disease – Reply. JAMA Neurology 2014;71(8):1054-1055 DOI:10.1001/jamaneurol.2014.15396001 | PRIU0000231 |
| 23 Nov 2012 | Sir Rory Collins letter of support to Professor John Collinge | WITN3093011 |
| 4 Mar 2013 | Correspondence between Dr Catherine Elliot and Professor Collinge regarding MRC contributing to funding | WITN3093012 |
| 13 Mar 2013 | Email from Dr Catherine Elliot regarding the decision from MRC Strategy Board | WITN3093013 |
| 8 May 2013 | Dr Elliot's response to PRIU000074, repeating opinion of the Strategy Board | WITN3093014 |

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| 16 Oct 2013 | Email exchange between Dr John Savill and Professor John Collinge regarding progressing the blood test | WITN3093015 |
| 2014 | After the storm? UK blood safety and the risk of variant Creutzfeldt-Jakob disease | **TSTC0000052** |
| 21 Jan 2016 | ACDP TSE Subgroup meeting | PHEN0002460_001 |
| Mar 2014 | Mead et al (2014) Variant Creutzfeldt-Jakob Disease With Extremely Low Lymphoreticular Deposition of Prion Protein | NCRU0000197_002 |
| 24 July 2014 | Sir John Savill's response to Professor Collinge regarding the report placing the ball firmly in the DoH's court | WITN3093016 |
| 30 Dec 2014 | Professor John Collinge's letter to Dame Sally Davies | WITN3093017 |
| 20 Jan 2015 | Dame Sally Davies' response to Professor John Collinge | WITN3093018 |
| 11 sMar 2015 | Letter from Dr Lorna Williamson and Dr Philip Minor to Mr Jolles | WITN3093019 |
| 13 May 2015 | Letter from Mr Jolles regarding discussed proposals | WITN3093020 |

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|---|---|---|
| June 2015 | Sawyer et al (2015) Preclinical detection of infectivity and disease-specific PrP in blood throughout the incubation period of prion disease | WITN3093021 |
| 2015 | Correspondence between Mr Jolles, colleagues at NHSBT, Marc Turner and Roland Salmon | WITN3093022 |
| 29 Sept 2016 | ACDP TSE Subgroup meeting | PHEN0002461 |
| 12 Dec 2016 | The response from the Policy Research Programme response that the application will not be considered any further | WITN3093023 |
| 2006 | Assessment to be carried out before surgery and/or endoscopy to identify patients with, or at increased risk of, CJD or vCJD - Annex J | WITN3093024 |
| 16 June 2016 | Professor John Collinge's presentation to the vCJD CGAG | WITN3093025 |
| Oct 1996 | Collinge et al (1996) Molecular analysis of prion strain variation and the aetiology of 'new variant' CJD | MHRA0021347 |
| 1997 | Hill et al (1997) diagnosis of new variant Cruetzfeldt-Jakob disease by tonsil biopsy | DHSC0004747_040 |

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|---|---|---|
| 2004 | Frosh et al. (2004) Analysis of 2000 consecutive UK tonsillectomy specimens for disease- related prion protein | RLIT0000727 |
| 2004 | Hilton et al. (2004) Prevalence of lymphoreticular prion protein accumulation in UK tissue samples | NHBT0063957_002 |
| June 2006 | Collinge et al (2006) Kuru in the 21st century—an acquired human prion disease with very long incubation periods | WITN3093026 |
| Aug 2000 | Hill et al (2000) Species-barrier-independent prion replication in apparently resistant species | DHSC0004808_059 |
| Mar 2020 | Gill O N et al. Prevalence in Britain of abnormal prion protein in human appendices before and after exposure to the cattle BSE epizootic. Acta Neuropathologica 2020; 139(6):965 | RLIT0000725 |
| 2017 | Mok et al (2017) Variant Creutzfeldt–Jakob Disease in a Patient with Heterozygosity at PRNP Codon 129 | WITN3093027 |
| 2005 | Mead et al (2005) letters to the editor regarding questionnaire to reduce risk of iatrogenic prion disease transmission | WITN3093028 |